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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
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DATE MAILED:

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 9/15/95 & 10/4/95 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-3, 5-8, 10-15, 37-42, 67-76 & 78 are pending in the application.
   Of the above, claims 67-76 are withdrawn from consideration.
2. ☒ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-3, 5-8, 10-15, 37-42 & 78 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

15. Claims 2, 4, 9-17, 20-36, 43-66 and 77 have been cancelled in response to applicant's amendment.

16. Claims 1, 3, 5, 6, 8, 19, 37-39, 41 and 42 have been amended.

17. Claims 1, 3, 5-8, 18, 19, 37-42, 67-76 and 78 are pending.

18. Claims 67-76 have been withdrawn as directed to a non-elected invention.

19. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

20. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make/use the invention, i.e. for failing to provide an enabling disclosure.

A) Applicant has not disclosed to one of ordinary skill in the art how to practice the claimed invention without undue experimentation. There is a high degree of unpredictability associated with methods claimed for the following reasons:

Waldmann [Science 252:1657-1662 (1991)] teaches that effective therapy using monoclonal antibodies has been elusive and describes limitations of murine antibodies in the therapy of human diseases due to the pharmacokinetic properties of rodent antibodies in human and human anti-mouse antibody responses. Waldmann also indicates that hopes for antibody-based treatment methods engendered by in-vitro and animal model studies have not correlated well with in-vivo clinical trail results in patients. Further Harris et al. [TIBTECH 11:42-46 (1993)] state "there is widespread acceptance that there is little future for the use of rodent mAbs for in vivo human therapy", see page 42, column 2, lines 3-7. Harris et al. also teach "the residual HAMA response to chimeric antibodies is mainly anti-idiotypic, therefore repeated dosing is ineffective", see page 42, column 3, lines 17-20. Applicant has only provide evidence of therapeutic use in nude mice, which are immunosuppressed. Nude mice therefore are not a sufficient model system to test anti-murine responses to antibodies. It is well known in the art that antibody-based therapies have very limited success. One of ordinary skill in the art would not readily accept that Applicant's claimed modified antibodies would be satisfactory for human therapy as asserted in the specification. As evidenced by Osband et al. [Immunotherapy 11(6):193-195 (1990)] one of ordinary skill in the art would not readily accept the utility of an immunotherapeutic agent without convincing objective evidence of efficacy in humans (see paragraph bridging pages 193-194). As further

evidenced by Waldmann and Dillman [Ann. Internal Med. 111:592-603 (1989)] it is well known in the art that the use of monoclonal antibodies has, in general, only met with very limited success in humans. Waldmann teaches that immunotoxins have not lived up to expectations and that "the results of in vivo clinical trials in patients with cancer with first-generation immunotoxins did not fulfill the hopes engendered by in vitro and animal model studies" (see page 1660, second column, fourth full paragraph). Dillman teaches that "as a therapeutic modality, monoclonal antibodies are still promising but their general use will be delayed for several years" (see Abstract). In addition, Hird et al. [Genes and Cancer (1990) chapter 17] teaches that "the data obtained from mouse studies are useful, but cannot be directly translated to apply to the human situation" (see page 185, first full paragraph). Other factors such as proteolytic degradation, immunological inactivation, antigenic modulation or antigen shedding by the tumor, as well as factors influencing localization of the antibody such as the anatomical location of the tumor and its vascularity and blood flow, all have bearing on the efficacy of the antibody therapy. Further, with respect to immunotoxins, the level of antigen expression and the rate and route of internalization also effect the therapeutic efficacy of the antibody. Given the teachings of Osband et al., Waldmann, Dillman, Hird et al. and Harris et al. as well as the other well known factors effecting antibody therapies, one of ordinary skill in the art would not readily accept Applicant's claimed utility on its face, absent some showing of convincing objective evidence of therapeutic or diagnostic utility. Therefore, the claims are rejected as lacking patentable utility. Further, regarding proteins in general - there is a high degree of unpredictability associated with the use of proteins in vivo: (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half life of the protein; (2) the protein may otherwise not reach the target area because, for example, (a) the protein may not be able to cross the mucosa, (b) the protein may be adsorbed or absorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo use.

Applicant contends, citing Thorpe TibTech 11:40-43 (1993), that monoclonal antibodies are useful as therapeutic agents and in vivo diagnostic agents. Applicant is invited to consider, Harris et al. which follows the Thorpe citation in the same journal at pages 44-46, previously made of record. Harris et al. state "there is widespread acceptance that there is little future for the use of rodent mAbs for in vivo human therapy", see page 42, column 2, lines 3-7. Harris et al. also teach "the residual HAMA response to chimeric antibodies is mainly anti-idiotypic, therefore repeated dosing is ineffective", see page 42, column 3, lines 17-20. Clearly, there is reason to believe that there is a high level of unpredictability in the field, especially when evidenced by two conflicting reports from different meeting published in the same journal. Applicant suggests in response to the utility rejection, now withdrawn, that the burden of proof shifts to the applicant only if there is a reasonable doubt as to the truth of the applicant's assertions not just any doubt. The references already of record in addition to those presented by applicant provide overwhelming evidence that there is a high degree of unpredictability associated with the claimed invention. Applicant response to the

Dillman, Hird and Osband references by stating that the claimed invention is not directed to cancer treatment. But, for the most part the general teachings presented in these references, regarding the application of antibodies, is applicable to any in vivo method. Applicant has provided Brusick, The role of animals in biomedical research [exhibit 3] and Rawlins. Long-Term Animal Studies: Their Predictive Value for Man [exhibit 4] arguing that in vitro studies demonstrate a reasonable correlation between in vitro and in vivo use. Brusick is addressing safety issues and is not concerned with whether the agent actually works or not. Rawlins, while also concerned with safety issues, expressly states that "the information provided by animal pharmacology tests is the most important part of preclinical program. . . ." [Page 18, last full paragraph]. Applicant states at page 11 of the response that they have taught that administration of the B7 antigen will result in effects similar to the use of anti-CD28 monoclonal antibodies reactive with the CD28 receptor in vivo. However, upon review of the specification applicant presents no objective evidence to support this allegation. In fact, there is no in vivo data presented in the specification. It remains unclear, give the extreme unpredictability of the agents of the claimed methods how such an allegation can be made with out substantiating evidence. The unpredictable nature of the agents involved in the claimed invention are such that a determination must be made on a case by case basis. In this case a reasonable correlation between the in vitro results provided and in vivo use has not been provided. Applicant suggests that adoptive immunotherapy is encompassed by the claimed method. Applicant is invited to review Basse et al. [Cancer Immunol. Immunother. 34:221-227 (1992)]. Basse et al. teach that while adoptive immunotherapy has proven successful in many animal models the clinical studies have been less encouraging with response rates of 20% or more observed only for melanomas and renal cell carcinomas. The arguments related to the B7Ig and CD28Ig fusion proteins is not persuasive. In vitro studies do not account for the unpredictable nature of the in vivo environment. For example: (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half life of the protein; (2) the protein may otherwise not reach the target area because, for example, (a) the protein may not be able to cross the mucosa, (b) the protein may be adsorbed or absorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo use. Thus, applicant has failed to adequately teach how to use the invention. The specification does not enable a person of ordinary skill in the art to practice the claimed invention without undue experimentation. The breath of the claims is drawn to in vivo use. Even if it were drawn to in vitro use the specification alleges that such use would be for adoptive immunotherapy which is unpredictable.

Applicant has provided several arguments regarding the above objection. However, applicant has not provided evidence to support these positions. Applicant points to in vitro data observed in Figure 16, however, from the above discussion this data is not predictive of the dynamic nature of the in vivo system. This objection still stands.

B) Applicant's specification does not support a method of inhibiting T cell proliferation with any B7 antigen derivative. Specifically, B7 on CHO cells, or immobilized in any way will not result in a method of inhibiting. Instead, such a B7 derivative will cross-link the CD28 receptor resulting in T cell activation and increased proliferation. Applicant misses the point - by stating the specification teaches B7Ig. The point was to have applicant limit the claimed invention limited to B7Ig. Applicant's comments were considered but were not found persuasive.

Applicant states that they are entitled to more than B7Ig and do not need to enable all possible embodiments of the invention. However, since B7 is a membrane receptor protein, it is unclear from the record and art in the field if this membrane receptor will function as claimed in a form other than the B7Ig. Membrane proteins will fold in a manner preculding their activity when seperated from the membrane. The prior art recognizes that the extracellular portion of membrane proteins can be solubilized with the Ig constant domains. Applicant has not provided any evidence in this record to demonstrate that the art would appreciate that other forms of the B7 protein can be used. This objection still stands.

C) The specification does not enable a method of inhibiting proliferation using an intact antibody molecule to the CD28 receptor. At page 47 of the specification applicant states that the inhibitory effects of anti-CD28 mAb 9.3 on the MLR responses on T cells are consistent with previous observations reported by Damle et al., J. Immunol. 120:1753 (1988). Damle et al. teach the inhibitory effect of anti-CD28 mAb in the MLR was reversed by cross-linking of anti-CD28 mAb with anti-mouse κ mAb. Since applicant's invention is not limited to in vitro use it would be expected that the anti-CD28 mAb would be cross-linked in vitro thereby activating the T-cell. Applicant's comments were considered but were not found persuasive.

Applicant appears to ignore the fact that accessory cells will bind the antibody resulting in the cross-linking of the receptor through the antibody. This phenomena will occur in vivo. Therefore Damle's results will be attained in vivo. This objection still stands.

I) The specification does not contemplate the CTLA-4 molecule. Thus even if the CD28/B7 interaction is inhibiting the CTLA-4/B7 interaction can still activate T cells. Applicant is encouraged to consider Linsley et al. [J. Exp. Med. 174:561-569 (1991)]. Applicant argues that the claimed invention is not directed to inhibiting T cell proliferation using all possible pathways. However, the objection is directed to the unpredictability of the claimed invention. Applicant suggests that T cell proliferation can be inhibited using a molecule which binds CD28. Since CTLA-4, a homologue, of CD28 is present on T cells it remains unclear if applicant can accomplish the inhibition claimed. CTLA-4 offers a second pathway for activation of T cells, thus even though the CD28/B7 interaction is prevented the CTLA-4/B7 interaction can result in activation of T cells irregardless of applicant's claimed method. Applicant's comments were considered but were not found persuasive.

Applicant argues that they do not need to demonstrate all possible mechanisms. However, this does not address the problem. The problem is there are several pathways for activation of T-cells. CTLA-4 is one. Applicant does not address the problem associated with CTLA-4 which will activate proliferation even if the CD28 receptor is bound. This objection still stands.

21. Claims 1, 3, 5-8, 18, 19, 37-42 and 78 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification. This rejection still stands, for the reasons given above.

22.. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

23. Claims 1 and 37-39 are rejected under 35 U.S.C. § 102(b) as being anticipated by Ledbetter et al. [J.I. 135(4):2331-2335 (1985)]. Ledbetter et al. teach Fab fragments of anti-TP44(CD28) were ineffective in inducing T cell proliferation, see abstract. These antibody Fab fragments will inherently block the interaction between CD28 and B7. The Fab fragment is derived from monoclonal antibody 9.3. Applicant contends that since Ledbetter et al. teach activation of T cell proliferation the statement in the reference that Fab fragments of the 9.3 antibody was ineffective in inducing T cell proliferation is not suggestive of inhibition of proliferation. Read in context Ledbetter et al. teach that the use of a Fab fragment did not result in T cell activation. Given that a Fab fragment when bound to an antigen will inhibit binding of another molecule Ledbetter et al. clearly teaches inhibition of T cell proliferation. Applicant states that since the interaction between CD28 and B7 was not known prior to the date of the claimed invention a suggestion that a Fab fragment would inherently block the interaction between CD28 and B7 represents hindsight reconstruction. To the contrary, a Fab to CD28 will inhibit T cell proliferation due to blocking any ligand, including B7, from binding the CD28 receptor while the Fab is bound. It is not necessary for recognition of the B7 ligand to be known, the Fab will block any CD28 ligand, inherently including B7.

Applicant states that "nowhere does Ledbetter teach that anti-CD28 M|Abs inhibit T cell proliferation. Applicant is invited to consider the abstract. Applicant continues by addressing the inherency position. It appears that the only difference between the Ledbetter et al. reference and the claimed invention is that the invention is further characterized. However, the underlying mechanism is the same. Therefore, this rejection therefore still stands.

24. Claims 1 and 37-40 are rejected under 35 U.S.C. § 102(b) as being anticipated by

Damle et al. [J.I. 140(6):1753-1761(1988)]. Damle et al. teach Fab fragments of anti-TP44(CD28) were ineffective in inducing T cell proliferation, see abstract. These antibody Fab fragments will inherently block the interaction between CD28 and B7. The Fab fragment is derived from monoclonal antibody 9.3.

Applicant points out that this rejection was previously made and withdrawn. Applicant is invited to note that the rejection was previously withdrawn in response to claim amendments. The claims have not been amended to define an invention described by Damle et al. Therefore the rejection is consistent. It appears that the only difference between the Ledbetter et al. reference and the claimed invention is that the invention is further characterized. However, the underlying mechanism is the same. Therefore, this rejection therefore still stands.

25. No claims allowed.

26. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

27. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4227.

28. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donald E. Adams whose telephone number is (703) 308-0570. The examiner can normally be reached Monday through Thursday from 7:30 to 6:00. A message may be left on the examiners voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. Margaret Moskowitz Parr can

be reached at (703) 308-2554. The fax phone number for Group 1806 is (703) 305-7401. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

December 22, 1995

Donald E. Adams, Ph.D.
Primary Examiner
Group 1800